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EFFECT OF CENTRAL NEUROTROPIC SUBSTANCES ON THE HYPOPHYSIS-
ADRENAL CORTEX SYSTEM DURING THE IMMOBILIZATION OF ANIMALS

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16. Abstract The immobilization of guinea pigs for 5, 12, 24 and 48 hours, by securing to a slab, results in a persistent rise of the blood plasma 17-oxy corticosteroid concentration. Repeated administration of phenobarbital (50 mg/kg) and of the sodium salt of γ-oxybutyric acid (500 mg/kg), as well as the combined administration of central m- and n-cholinolytics with small doses of phenobarbital tends to inhibit activation of the adrenal cortex during 48 hour immobilization of the animals. Repeated administration of aminazine (20 mg/kg) tends to decrease activation of the adrenal cortex. The administration of reserpine (0.1-5 mg/kg) 12-18 hours before immobilization of guinea pigs increases the response of the hypophysis-adrenal cortex system.			
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EFFECT OF CENTRAL NEUROTROPIC SUBSTANCES ON THE HYPOPHYSIS-ADRENAL CORTEX SYSTEM DURING THE IMMOBILIZATION OF ANIMALS

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The immobilization of animals is widely used in experiments, as an extreme neurogenic stimulus [15, 4, 13, 20, 1, et al]. It has been determined that the hypophysis-adrenal system is activated during immobilization [15, 17, 18, 14 et al]. In study of the central mechanisms of this activation, the use of neurotropic substances which selectively affect different sections of the brain and its biochemical systems can be of great assistance.

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The effect of central neurotropic substances on the hypophysis-adrenal cortex system of immobilized guinea pigs was studied in this work. "Central" and "cortical" sedatives, as well as the sodium salt of γ -oxybutyric acid, were used. Besides, substances which depress the central cholinergic, adrenergic and serotonergic systems, as well as antihistamines were studied.

Method

The tests were conducted on 328 male guinea pigs weighing 300-400 g. The animals were immobilized by securing them to a slab for various periods (5, 12, 24, 48 hours). The state of the hypophysis-adrenal cortex system was decided from the concentration of 17-oxy-corticosteroids (17-OCS).

The latter was determined by the method of N.A. Yudayev and Yu.A. Pankov [19], in the plasma of blood obtained from the heart. The test substances were administered repeatedly under the skin (every 8-10 hours during long term immobilization). To check the state of the adrenal cortex reserves, ACTH was administered (5 units intraperitoneally).

*Numbers in the margin indicate pagination in the foreign text.

For each test, 8-10 animals were used. The results were processed statistically.

Results

The plasma 17-OCS concentration of blood obtained from the heart of intact male guinea pigs, kept in vivaria for 1-2 weeks, was 50.8 ± 6.2 $\mu\text{g}\%$. Immobilization of the animals for 5, 12, 24 and 48 hours resulted in a considerable increase in the 17-OCS concentration in the blood plasma (Fig. 1). The repeated administration of 5 units of ACTH to guinea pigs immobilized for 48 hours caused only a small further increase in the blood 17-OCS concentration. This indicates prolonged, almost maximum stimulation of the adrenal cortex during immobilization.

Study of the effect of neurotropic substances on the 17-OCS concentration was carried out during 48 hour immobilization of the animals. We chose this period of immobilization, because, during neurogenic stimulation of the hypophysis-adrenal system, test substances could be administered repeatedly. Some authors place great importance on the repeated use of neurotropic substances in study of their effect on the hypophysis-adrenal system [7, 2 et al].

The "central" sedative phenobarbital, administered repeatedly every 10 hours at a dose of 50 mg/kg, definitely reduced the hypophysis-adrenal system activity during immobilization. At lower doses (25 mg/kg), the preparation had little effect. The "cortical" sedative chloral hydrate, used at a dose of 300 mg/kg every 10 hours, did not have a similar effect. Repeated (every 10 hours) administration of the test sedatives to guinea pigs, at the doses used during immobilization, was accompanied by a narcotic effect (the animals did not react to painful stimuli, noise, etc.). The sodium salt of the γ -oxybutyric acid, administered at a dose of 500 mg/kg, induced a subnarcotic state in the animals, and it had a definite depressant activity in the adrenal cortex during immobilization. The use of the preparation at smaller doses (50-200 mg/kg) was ineffective. In the administration of the central /546

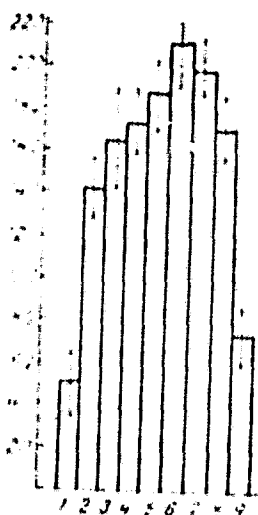


Fig. 1. Effect of immobilization and ACTH on 17-oxy-corticosteroid concentration of guinea pig blood plasma.

Ordinate, 17-OCS concentration in µg%. Each bar represents 8-10 determinations.

1. 17-OCS concentration in control animals; 2,3,4,5. in animals immobilized 5, 12, 24, 48 hours, respectively; 6. in animals immobilized 48 hours + ACTH every 8-10 hours; 7. in immobilized, starved animals + ACTH every 8-10 hours; 8. in immobilized, unstarved animals + ACTH every 8-10 hours; 9. in animals starved 48 hours.

m-cholinolytic methamizyl, it was determined that, at a dose of 3 mg/kg, it somewhat slowed down activation of the adrenal cortex of immobilized animals. Upon increasing the dose to 20 mg/kg, this effect was not displayed. Administration of the central n-cholinolytic spasmolytin (5-20 mg/kg) did not cause changes in the response of the adrenal cortex. However, by the combined administration of central m- or n-cholinolytics with doses of phenobarbital of little effect (25 mg/kg), distinct depression of the response of the hypophysis-adrenal systems of immobilized guinea pigs was observed (Fig. 2).

Repeated administration of aminazine (5-10 mg/kg) did not show a positive change in the degree of activation of the hypophysis-adrenal system. At a dose of 20 mg/kg, aminazine somewhat reduced this activity (see Fig. 2). Diprazine, a preparation with a marked antihistamine effect, used at a dose of 20 mg/kg, did not have a definite effect.

Reserpine was studied in subsequent tests, at a dose of 1-2.5 mg/kg. According to the data of a number of authors [11, 3, 4], the use of reserpine at these doses in

an experiment leads to a 50-100% drop in the norepinephrine and serotonin content of the brains of rats and rabbits, in 2-30 hours. Reserpine was administered 12-18 hours before immobilization. It was noted that, 18-24 hours from the start of immobilization, a considerable portion of the guinea pigs died. The administration of small doses of reserpine (0.2 mg/kg), 12 hours before immobilization and repeatedly during 48 hour immobilization, also was accompanied by the death of a

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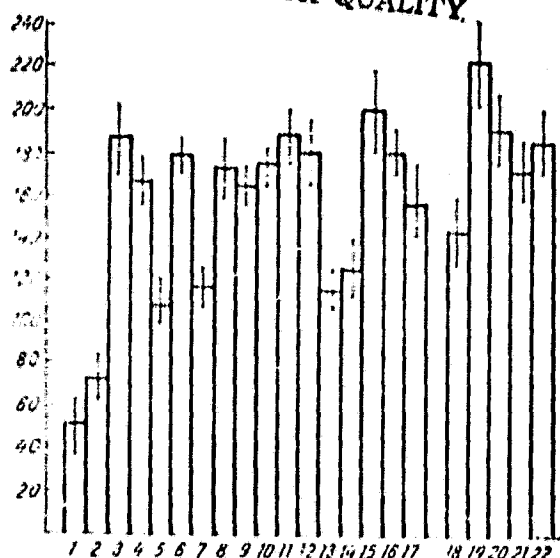


Fig. 2. Effect of neurotropic substances on 17-OCS concentration in blood plasma of guinea pigs immobilized 48 hours. 1. 17-OCS concentration in control animals; 2. in animals starved 48 hours; 3. in animals immobilized 48 hours; 4,5. in animals receiving 25 and 50 mg/kg doses of phenobarbital; 6. in animals receiving chloral hydrate (300 mg/kg); 7. in animals receiving sodium salt of γ -oxybutyric acid (500 mg/kg); 8,9,10,11. in animals receiving 1, 3, 10 and 20 mg/kg methamizyl; 12. in animals receiving spasmolytin (20 mg/kg); 13. in animals receiving methamizyl (10 mg/kg) + phenobarbital (25 mg/kg); 14. in animals receiving spasmolytin (20 mg/kg) + phenobarbital (25 mg/kg); 15, 16,17. in animals receiving 5, 10 and 20 mg/kg doses of aminazine; 18. 17-OCS concentration in animals immobilized 5 hours; 19,20, 21,22. in animals receiving 0.1, 1, 2.5 and 5 mg/kg doses of reserpine; remaining designations same as in Fig. 1.

portion of the animals. Therefore, to determine the effect of the administration of reserpine to the animals on activation of the hypophysis-adrenal cortex system during immobilization, tests were conducted, with limitation of the immobilization period to 5 hours. Reserpine was administered after 12-18 hours, at doses of 0.1-5 mg/kg. It was determined that, at the doses of reserpine used, the response of the adrenal cortex of guinea pigs immobilized for 5 hours was increased.

Discussion of Results

Depression of the response of the hypophysis-adrenal cortex system by the "central" sedative phenobarbital, and the absence of such an effect of the "cortical" sedative chloral hydrate indicate the primary importance of the central sections of the brain in activation of this system during immobilization of guinea pigs. This is consistent with the data of a number of authors, who observed depression of the hypophysis-adrenal system by barbiturates in other types of neurogenic exposures [5, 6, 12, 10 et al]. Depression of the response of the

adrenal cortex by large doses of the sodium salt of γ -oxybutyric acid apparently should be connected with the capacity of the preparation to

have a marked depriving effect on various sections of the central nervous system by resorptive action [8, 9, 16 et al].

The results obtained with the use of central cholinolytics show that the m-cholinolytic methamizyl, repeatedly administered at a dose of 3 mg/kg, somewhat inhibits the increase in 17-OCS concentration in immobilized animals. Methamizyl more effectively depresses the hypophysis-adrenal system, by its use with small (ineffective) doses of phenobarbital. It should be noted that the combined effect of inactive doses of the central n-cholinolytic spasmolytin and phenobarbital result- /548 ed in depression of the response of the adrenal cortex of immobilized animals. These data indicate the participation of the central m- and n-cholinergic systems in the mechanism of activation of the hypophysis-adrenal cortex system during immobilization.

The results of the tests with the use of reserpine show that, with considerable reduction of the norepinephrine and serotonin content of the brain, the hypophysis-adrenal cortex system responds (and even increases somewhat) to a neurogenic stimulus. The absence of a positive effect of the antihistamine preparation diprazyl on activation of the hypophysis-adrenal cortex system during immobilization shows that the possible role of histamine in this activation is small.

Conclusions

1. The immobilization of guinea pigs for various periods (5, 12, 24, 48 hours) results in a persistent increase in the 17-oxy-corticosteroid concentration in blood plasma.

2. The "central" sedative phenobarbital, in distinction from the "cortical" chloral hydrate, depresses the response of the hypophysis-adrenal system of immobilized guinea pigs.

3. Central m- and n-cholinolytics (methamizyl and spasmolytin respectively), upon repeated administration with small (ineffective) doses of phenobarbital, reduced the response of the adrenal cortex of

immobilized animals.

4. Large doses of sodium oxybutyrate (500 mg/kg) decreases the activity of the adrenal cortex of immobilized guinea pigs.

5. Repeated administration of aminazine, at a dose of 20 mg/kg, has a tendency to decrease activation of the adrenal cortex.

6. The administration of reserpine (0.1-5 mg/kg), 12-18 hours before immobilization of guinea pigs, increases the response of the hypophysis-adrenal cortex system.

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